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Brief Clinical Report

Giant-Cell Chondrodysplasia in a Male Infant With Clinical and Radiological Findings Resembling the Piepkorn Type of Lethal Osteochondrodysplasia

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We report on a patient whose clinical, radiologic, and histopathologic findings are compatible with the Piepkorn type of lethal short-limb osteochondrodysplasia, but who also showed multinucleated giant chondrocytes in cartilage. Multinucleated giant cells are an unusual finding in osteochondrodysplasias, having been reported in atelosteogenesis type I and boomerang dysplasia. This uncommon histopathologic finding and the clinical and radiographic findings strongly support the diagnosis of boomerang dysplasia in the present patient. Our patient supports the previously suggested existence of an entity including atelosteogenesis and boomerang dysplasia. If this is so, the current patient and that described by Piepkorn et al. [1977: Teratology 16:345–350] could represent the most severe clinical expression of that condition. Am. J. Med. Genet. 68:342–346, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: giant-cell osteochondrodysplasia; Piepkorn syndrome; boomerang dysplasia; atelosteogenesis type I; frontonasal malformation; frontonasal dysplasia; osteochondrodysplasia

INTRODUCTION

Piepkorn et al. [1977] described a patient with a lethal neonatal osteochondrodysplasia comprising extremely short limbs and ribs, polysyndactyly, craniosynostosis, cleft palate, cardiovascular and urogenital defects, and defective ossification. A similar case was reported by Canki-Klain et al. [1992]. This entity was classified as a new type of short rib-polydactyly syndrome [Piepkorn et al., 1977; Cherstvoy et al., 1980], and more recently it was considered a severe form of boomerang dysplasia [Spranger and Maroteaux, 1990; Winship et al., 1990; Hunter and Carpenter, 1991; Canki-Klain et al., 1992].

The presence of multinucleated giant chondrocytes in resting cartilage is an unusual histologic finding in the osteochondrodysplasias. First observed by Battin et al. [1977] in twins with an unclassified form of spondyloepiphyseal dysplasia, it has been reported in some cases with atelosteogenesis type I (AT-I) [Sillence et al., 1982; Yang et al., 1983], and in boomerang dysplasia [Kozlowski et al., 1981; Hunter and Carpenter, 1991]. Piepkorn et al. [1977] did not observe multinucleated giant chondrocytes in the skeletal tissue of their case.

We report on a patient whose clinical and radiographic manifestations were very similar to those described by Piepkorn et al. [1977]. However, histopathologic examination of the limb bones in our patient demonstrated the presence of multinucleated giant chondrocytes. This observation adds new data to support the current interpretation of Piepkorn dysplasia as a severe form of boomerang dysplasia.

CLINICAL REPORT

The propositus was ascertained through the Spanish Collaborative Study of Congenital Malformations [Martínez-Frias and Urioste, 1994]. The male infant was the product of the first pregnancy of a 27-year-old mother and 33-year-old father, both healthy and nonconsanguineous. This couple had a second pregnancy

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that ended in an apparently normal baby. Family history was unremarkable. The gestation was complicated by oligohydramnios and an upper respiratory tract infection in the fourth month which was treated with "antigrippal" drugs. There was no history of exposure to known or suspected environmental teratogens during pregnancy. Delivery was induced at 27 weeks of gestation. Birth measurements were: weight 910 g (25th centile), crown–rump length 20 cm (<3rd centile), occipito-frontal circumference (OFC) 24 cm (25th centile), and chest circumference 12 cm (<<3rd centile). This was a markedly disproportionate infant with a large head and very short limbs and generalized alopecia (Figs. 1, 2). The head was brachycephalic with flat occiput, wide anterior fontanel, and striking frontal bulging (Fig. 2). There was severe true hypertelorism with protruding eyes and absence of eyelids and eyebrows. The nose was hidden by the frontal prominence and the nares were narrow. The mouth was small with a cupid-bow upper lip, and there was a left cleft lip without cleft palate, and severe micrognathia. There were apparently low-set and malformed ears and short neck with an extra fold of skin. The trunk appeared edematous with a narrow chest and protuberant abdomen. There were wide-spaced and rudimentary nipples, omphalocele, cryptorchidism, and small penis (Fig. 2). The limbs were very short with "flipper-like" appearance. The first fingers were rudimentary and the other four were fused and markedly hypoplastic. The toes were also rudimentary.

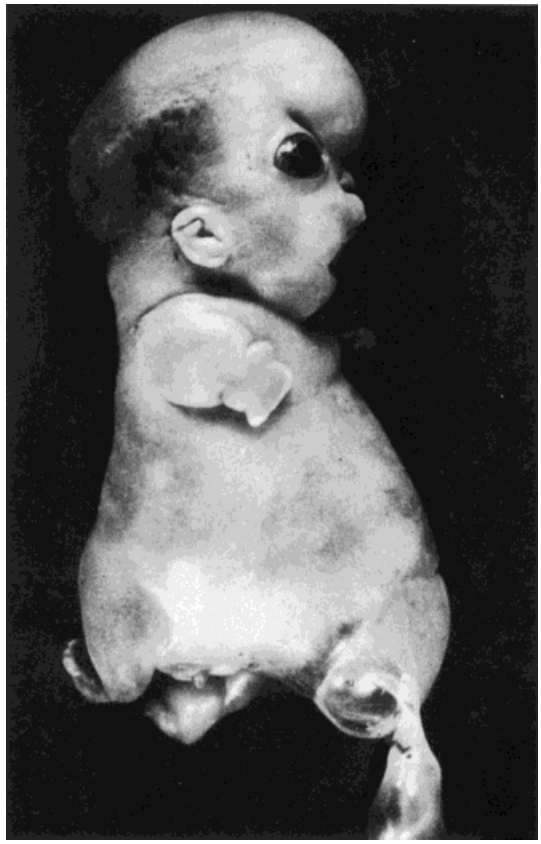

Fig. 2. Lateral view of patient.

Fig. 1. Frontal view of patient.

Radiological examination showed generalized underossification (Figs. 3, 4), except in the sphenoid wings and other structures of the cranial base. There was a cranium bifidum occultum. The clavicles were broad, bowed, and well-ossified. The scapulae has a notch at the glenoid cavity. A small, round ossification center was seen in the left forearm. The vertebral bodies were not ossified, except in three or four cervical vertebrae, whereas the lateral pedicles were seen throughout the spine (Fig. 3). The thorax was bell-shaped. There were three bodies of the sternum and 11 pairs of ribs. The pelvis was rudimentary (Fig. 4). The iliac wings were rounded with supracetabular narrowing. The iliac bodies showed a better ossification. The ischia were square with a stellate contour. The pubic bones were absent. Only one well-ossified and bowed bone was observed in the legs (Fig. 4), which had the appearance of a "boomerang" and corresponded in position to the tibia. These bones showed distal metaphyseal spurs.

Upper and lower limbs were removed for histological study. The upper-limb sections showed rounded cartilage masses which lacked any evidence of endochondral or membranous bone formation. Similar changes were seen in all cartilage pieces. Chondrocytes showed a fairly even distribution in the perichondrial zones,

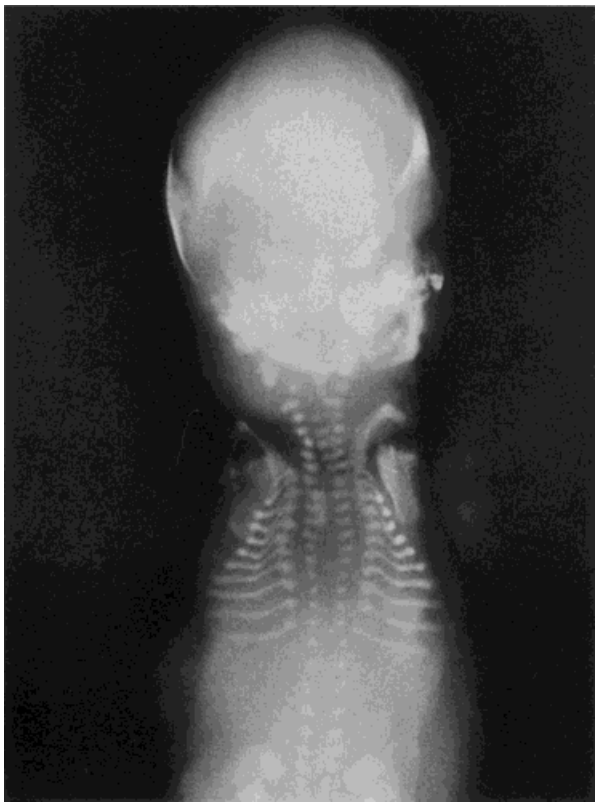

Fig. 3. Radiographic features of the cranium and thorax.

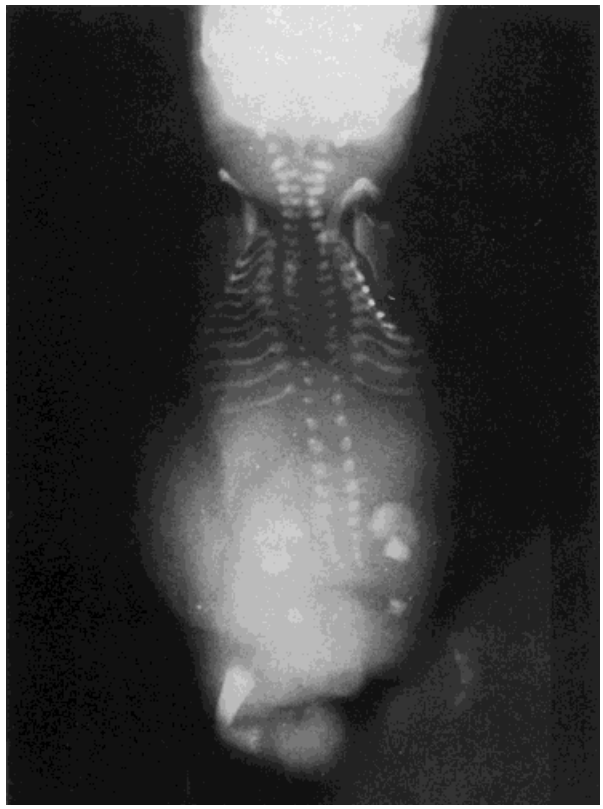

Fig. 4. Radiograph of the pelvis and lower limbs.

while cell clustering, irregular matrix degeneration with small cystic areas, and multinucleated cells were seen in the central parts of the cartilages. Variations in number of nuclei and in cell size and shape were observed in multinucleated cells (Fig. 5). Some had two oval nuclei and normal-sized cytoplasms, and others were true "giant cells" with up to five lobulated nuclei and very large cytoplasms with pale vacuoles (Fig. 6).

Some differences were observed between the lower- and upper-limb sections. The proximal lower-limb skeletal piece had a bony shaft and cartilaginous epiphysis with progressive maturation through resting cartilage, proliferative zone, and hypertrophic zone (Fig. 7). However, both bone trabeculae and the growth plate showed many abnormalities. In the plate, multiple areas of fibrillar and hypocellular cartilaginous matrix existed; in the lower proliferative zone and hypertrophic zone, the matrix was reduced in amount; hypertrophic chondrocytes were larger than expected; and cellular columnization, vascular invasion, and metaphyseal bone formation were absent. In the bone (Fig. 8), osteocytes were increased in number and size, and bone trabeculae were thick and composed of immature matrix. In addition, multinucleated cells and giant chondrocytes, and acellular areas, were more frequent in lower-limb cartilages than those of the upper limbs.

Chromosome studies were carried out on chondrocyte culture [Urioste, 1993]. Cell growth was peculiarly good and, subsequently, first harvesting could be done 3 days after culture initiation. Karyotype was apparently normal (46,XY). The percentage of polyploidy was no different than that observed in other chondrocyte cultures.

DISCUSSION

Piepkorn et al. [1977] described a female infant with an unique multiple congenital anomalies pattern. Phenotypically, the infant exhibited severe craniofacial anomalies including a brachycephalic head, a large and

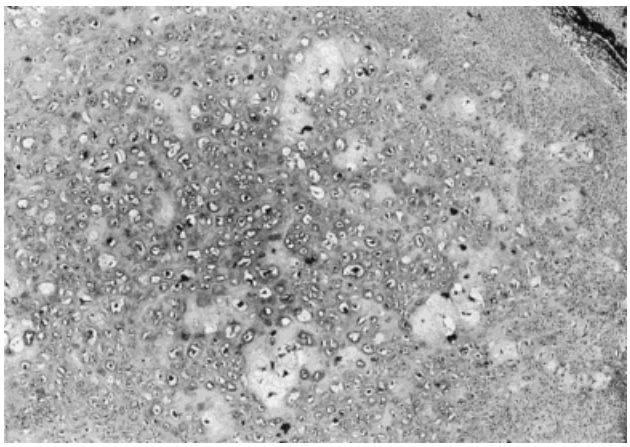

Fig. 5. Cartilage from upper limb, showing irregular-sized chondrocytes and scattered matrix degeneration.

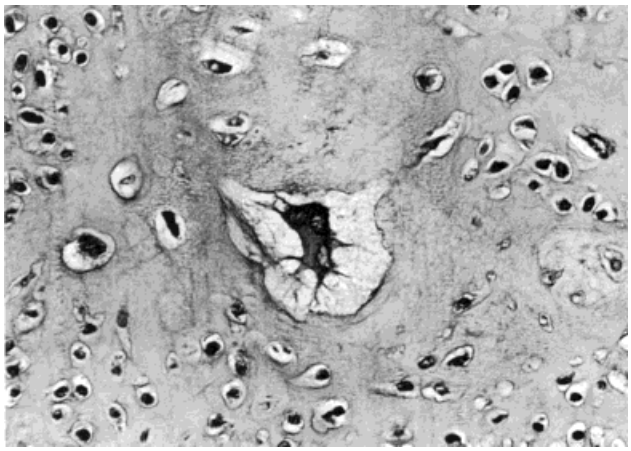

Fig. 6. High-power magnification of upper-limb cartilage, showing multinucleated giant cells. Original magnification × 250.

Fig. 8. Metaphyseal bone, showing thick trabeculae without laminar collagen organization.

bulging anterior fontanel, hypertelorism, absence of eyelashes and eyebrows, sunken and presumably bifid nose (Fig. 2 of Piepkorn et al. [1977]), and small mouth with cleft palate. Other external anomalies were prominent abdomen, vaginal atresia, flipper-like arms and feet, polydactyly, and fused fingers. Internal abnormalities included hypoplasia of the epiglottis, larynx, and tracheobronchial tree, cardiovascular and urogenital anomalies, and arrhinencephaly. Radiographic findings included short ribs, and severe underossification of all bones except the base of the skull and the clavicles. An unusual ossification pattern, but without giant chondrocytes, was recognized in the histological analysis of the cartilage.

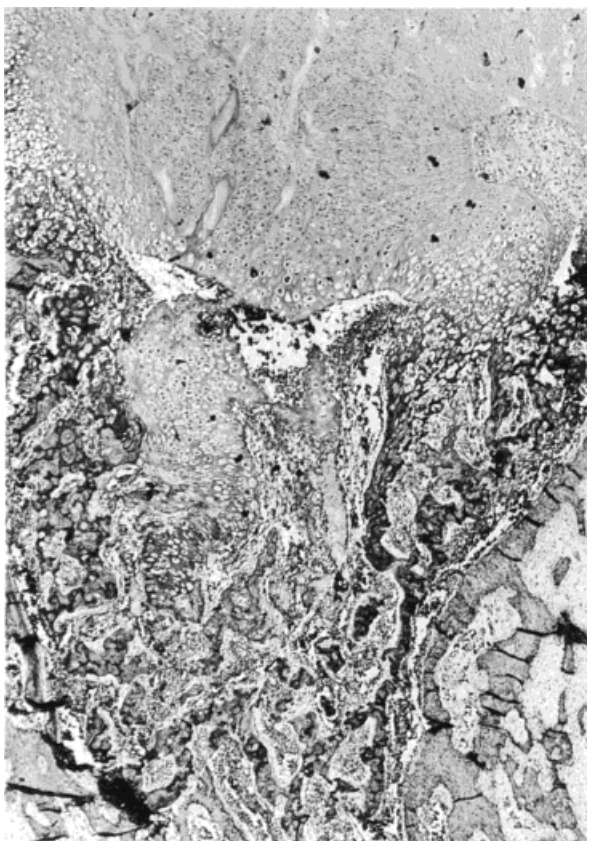

Fig. 7. Cartilage and bone junction of lower limb, with distortion of growth plate.

Canki-Klain et al. [1992] reported a patient with a lethal form of osteochondrodysplasia identical to the case described by Piepkorn et al. [1977].

The present patient had a very similar phenotype and almost the same radiological findings as the two above-mentioned cases. He had very short arms and legs (flipper-like appearance), a relatively large head, true hypertelorism, a striking frontal prominence, small nose and mouth, and generalized alopecia. The most remarkable radiological finding was severe underossification, most evident in cranial vault, vertebral bodies, and long bones, and better ossificated clavicles and cranial base. Although our patient had neither internal anomalies nor ploydactyly, all 3 patients could have been affected by the same condition with a variation in degree of severity.

It is noteworthy that all 3 patients had a set of craniofacial anomalies compatible with a median cleft face anomaly (MCFA) [DeMyer, 1967], or a frontonasal malformation (FNM) [Gorlin et al., 1990]. MCFA/FNM consists of hypertelorism, cranium bifidum occultum, broad nasal root, and a median cleft of the nose and/or upper lip and/or palate in varying degrees [Hennekam et al., 1986; Gorlin et al., 1990]. It is considered a nonspecific developmental field defect [Gorlin et al., 1990], and as such it was reported as an isolated and sporadic defect [DeMyer, 1967] and in syndromes of different causes [Chen et al., 1987; Toriello et al., 1985]. However, as far as we know, MCFA/FNM has not been reported previously as a manifestation of an osteochondrodysplasia, although Gorlin et al. [1990] stated that facial appearance in boomerang dysplasia is similar to that seen in frontonasal malformation.

Spranger and Maroteaux [1990] and Winship et al. [1990] reinterpreted the report by Piepkorn et al. [1977] to indicate a severe form of boomerang dyspla-

sia. Boomerang dysplasia is a recently delineated form of neonatally lethal osteochondrodysplasia. Only 4 cases have been documented to date [Kozlowski et al., 1981, 1985; Tenconi et al., 1983; Winship et al., 1990]. The most salient clinical findings in this condition are severe shortness of all four limbs with normal or large head, wide forehead, hypertelorism, exomphalos, and soft-tissue syndactyly. Generalized underossification, absence of several bones, and modelling in a boomerang shape of other long bones are radiological characteristics of boomerang dysplasia. The present patient, and those of Piepkorn et al. [1977] and Canki-Klain et al. [1992], shared many of the manifestations of boomerang dysplasia. Furthermore, our patient and that of Canki-Klain et al. [1992] had giant chondrocytes in the resting cartilage, and this finding was also described in boomerang dysplasia [Kozlowski et al., 1985].

Multinucleated giant chondrocytes are a causally nonspecific histologic finding documented in AT-I [Sillence et al., 1982; Yang et al., 1983], in boomerang dysplasia [Kozlowski et al., 1985], and in two sporadic and atypical forms of spondyloepiphyseal dysplasia [Battin et al., 1977; Yang et al., 1983]. It is remarkable that AT-I and boomerang dysplasia have a substantial clinical, radiologic, and histopathologic overlap. Hunter and Carpenter [1991] reported on a patient with a severe form of AT-I who had some manifestations of boomerang dysplasia. These authors proposed that AT-I and boomerang dysplasia could be a single entity, probably with a common cause. Although further studies are needed to confirm this hypothesis, the most severe forms of this condition could be represented by the present patient, as well as by those described by Piepkorn et al. [1977] and Canki-Klain et al. [1992].

The pathogenesis of multinucleated giant chondrocytes is unknown. Battin et al. [1977] observed giant chondrocytes in the epiphyseal cartilage of twins with an atypical form of osteochondrodysplasia, and they suggested that these cells must be the result of a disturbance in a last step of cellular division. In the present case, polyploidy was not found in the chromosome study on cartilage. This is in agreement with the assumption by Battin et al. [1977], in the sense that multinucleated giant chondrocytes show serious difficulties in carrying out normal cell division and, subsequently, it may be uncommon to discover polyploidy metaphases in in vitro cultures.

Our patient may represent the seventh described case of boomerang dysplasia. In the ECEMC, the frequency of this condition is 1/1,222,698 liveborn infants surveyed from April 1976–March 1995. The cause is unknown. All reported cases are sporadic. If the case of Piepkorn et al. [1977] had a boomerang dysplasia, X-linked recessive inheritance is practically ruled out because the patient was female.

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